

## ***Remarks***

### ***I. Support for Amendments and Status of the Claims***

By the foregoing amendments, claim 50 is sought to be amended. Support for the amendments to claim 50 can be found throughout the application as originally filed, particularly at page 10, lines 15-29, and at page 16, line 5 through page 17, line 23. Hence, these amendments add no new matter, and their entry and consideration are respectfully requested. Upon entry of the foregoing amendments, claims 50-59 and 74-76 are pending in the application, with claim 50 being the sole independent claim.

### ***II. Summary of the Office Action***

In the Office Action, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks to overcome and/or traverse each of these elements of the Office Action.

### ***III. The Rejection Under 35 U.S.C. § 112, Second Paragraph***

In the Office Action at page 3, section 8, the Examiner has rejected claims 50-59 and 74-76 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that the recitation of "no more than about 10% non-tetrameric" in claim 50 renders this claim (and the remaining dependent claims) indefinite. Applicants respectfully disagree with this contention, and assert that one of

ordinary skill could readily understand the meaning of this recitation based on the teachings of the present specification in view of knowledge that is readily available in the art.

Notwithstanding this assertion, claim 50 has now been amended to recite a tetrameric uricase wherein at least about 90% of the uricase is in a tetrameric form. Hence, one of ordinary skill would readily understand that the uricase of claim 50 contains no more than about 10% *non-tetrameric uricase* (e.g., uricase in monomeric or dimeric form, or in any aggregated form larger than tetrameric), rather than no more than about 10% "impurities . . . [that] can be any material which is not tetrameric, or which may be any other compound or protein material; and contain *up to* 10% impurities." Office Action at page 3, section 8, second paragraph (emphasis in original). As the present specification clearly teaches at pages 10 and 16-17, and in Example 1 at pages 20-21, whether or not a given tetrameric uricase preparation contains at least about 90% uricase in a tetrameric form can be readily determined by one of ordinary skill using a variety of routine methods, including, *e.g.*, chromatographic methods such as those disclosed in the specification and that are known in the art. As the Board has held:

[35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

*Ex parte Moelands*, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (C.C.P.A. 1971)). Since the levels of non-tetrameric uricase present in a given tetrameric uricase preparation are easily determined using routine methods that are taught in

the specification and that are known in the art, one of ordinary skill could easily determine the scope of claim 50 as currently presented. Claim 50 thus comports with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*, and therefore is not indefinite.

In view of the foregoing remarks, Applicants respectfully assert that claims as currently presented particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, therefore are respectfully requested.

***IV. The Rejections Under 35 U.S.C. §§ 102(b) or 103(a) Over "Cheng"***

In the Office Action at pages 4-7, section 9, the Examiner has rejected claims 50-53 and 74-76 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over *Lee et al., Science* 239: 1288-1291 (1988) (of record as Doc. No. AT14; referred to by the Examiner in the Office Action, and hereinafter, as "Cheng"). Applicants respectfully traverse these rejections.

Cheng does not expressly or inherently disclose the production of a tetrameric uricase that has been purified such that it contains at least about 90% tetrameric uricase. Instead, Cheng discloses methods for cloning the cDNA of uricase using probes to an amino-terminal amino acid sequence for porcine uricase. Importantly, however, Cheng does not disclose the expression of the uricase protein.

Applicants note that Cheng mentions in passing that the authors obtained a commercially available uricase (Sigma Cat. No. U 3250) and "purified [it] to homogeneity."

Cheng at page 1289, col. 2, first full paragraph, and note 8 at page 1291, col. 1. As Applicants noted in the Reply filed in the present matter on December 11, 2003, at pages 26-28, uricase preparations such as those available from Sigma (including Sigma Cat. No. U 3250, the very commercially available uricase used in the studies in Cheng) contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. Put another way, the Sigma uricase used in Cheng does not contain uricase in which at least about 90% of the uricase is in a tetrameric form, as required by the present claims. Moreover, although Cheng reports that the Sigma uricase was "purified to homogeneity," this reference does *not* indicate that at least 90% of the "purified" uricase was in a tetrameric form. Indeed, the reference does not indicate in *what* form the "purified" uricase was, let alone that at least about 90% of it was in a tetrameric form.

As the present specification clearly teaches at page 16, lines 5-16, purified preparations of natural and recombinant uricase usually contain a mixture of forms of the enzyme, in addition to the tetrameric form. The estimated percentage of the non-tetrameric form of the enzyme present in such preparations varies from more than 10% to about 80%. *See id.* Hence, without specifically purifying their uricase preparations to enrich for the tetrameric form over all other forms, the authors of Cheng would not be expected to have produced a uricase preparation in which at least about 90% of the uricase is in a tetrameric form. Thus, as one of ordinary skill would readily appreciate, Cheng does not disclose the production of the presently claimed isolated tetrameric mammalian uricase.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly*

*Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The Examiner has pointed to no express disclosure in Cheng that would support the Examiner's statement that the uricase disclosed therein "is tetrameric and is substantially pure." Office Action at page 5. As noted above, Cheng does not disclose the production of a uricase in which at least about 90% of the uricase is in a tetrameric form. Thus, this reference cannot and does not anticipate the presently claimed invention.

Furthermore, in making this rejection, the Examiner contends that "protein aggregation is an intrinsic property of the protein and is depended [sic] upon the concentration of the protein in solution." Office Action at page 4, section 9, final paragraph. The Examiner further contends that "it would have been obvious for one of ordinary skill in the art to vary the aggregation percent by varying the purified protein(s) [cheng et al (1988) or Wu et al.] concentration by what is well known in the art of protein chemistry . . . ." Office Action at pages 5-6, section 9. Applicants respectfully disagree with these contentions.

As one of ordinary skill would readily appreciate, one is extremely unlikely to be able to produce a uricase preparation wherein at least about 90% of the uricase is in a tetrameric form simply by diluting the concentration of uricase in a given solution. Under standard

thermodynamic and solution chemistry principles, it would be more likely that some steady-state distribution between the various forms of uricase (monomers, dimers, tetramers, octamers, etc.) would result from such a dilution approach. A solution in which one form (*e.g.*, the tetrameric form) is so predominant as to make up at least about 90% of all of the uricase in the solution therefore is thermodynamically unlikely to develop if one simply dilutes a more concentrated form of uricase as the Examiner has suggested. Furthermore, even if such an approach *could* be used to produce a preparation of uricase in which at least about 90% of the uricase is in a tetrameric form, one of ordinary skill would have to undertake undue experimentation in order to determine *exactly* the level of dilution required to result in a preparation so enriched in the tetrameric form over all other forms. Accordingly, one of ordinary skill would have no reasonable expectation that by simply diluting a preparation of purified uricase, a preparation in which at least about 90% of the uricase is in the tetrameric form would be successfully produced.

To this end, the Examiner's attention is directed to the disclosure contained in WO 01/59078 (Doc. No. AN2 cited in Applicants' First Supplemental Information Disclosure Statement filed in the present matter on November 14, 2002) by some of the present inventors. Figures 2 and 3 (and particularly Figure 2) of this publication show clearly that uricase aggregates that are at too low a concentration in solution (*i.e.*, that are too dilute) to be detected by their ultraviolet absorbance at 276 nm (lower panels in Figures 2 and 3) are readily detected by a light scattering detector (upper panels in Figures 2 and 3) which detects aggregation of protein. Hence, aggregates larger than tetramers were present in these uricase solutions even when the uricase in these solutions was so highly diluted as to be unsuitable for

use as a therapeutic agent or for use as a substrate for efficient polymer coupling. Accordingly, contrary to the Examiner's assumption in making this rejection, simply diluting the uricase solution would not necessarily be expected to result in a preparation of uricase in which non-tetrameric aggregates are not present.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, for at least the reasons discussed above, the Examiner's burden has not been satisfied.

Moreover, the Examiner's contention that one of ordinary skill in the art would have been motivated to have combined Cheng with what is well known in the art of protein chemistry to make the presently claimed isolated uricase tetramer is not based on any actual

evidence or sound scientific reasoning available in the art. There is no disclosure in Cheng that could provide such guidance, nor in the abstract of Malakhova *et al.* cited and excerpted by the Examiner in the Office Action at pages 6-7. Hence, the Examiner has provided no sound scientific reasoning or other objective evidence to support the contention that it would have been obvious to vary the aggregation percent by simply varying the concentration of the purified protein by dilution.

As the Federal Circuit has held:

[t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

*In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). When the PTO relies upon "general knowledge to negate patentability . . . [such] knowledge must be articulated and placed on the record." *In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002). That is, "deficiencies of the cited references cannot be remedied by the [PTO]'s general conclusions about what is "basic knowledge" or "common sense."" *Id.* at 1344 (quoting *In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001)) (citation omitted). Since the Examiner has provided no actual evidence or sound scientific reasoning to support the conclusory statement that Cheng and "what is well known in the art of protein chemistry . . . ." in combination render the presently claimed invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

In view of the foregoing remarks, Applicants respectfully assert that Cheng does not anticipate, or in the alternative render obvious, claims 50-53 and 74-76 as currently presented.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102(b) or 103(a) over Cheng therefore are respectfully requested.

***VIII. The Rejection Under 35 U.S.C. §§ 102(b) or 103(a) Over Wu***

In the Office Action at page 4, section 9, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated, or in the alternative under 35 U.S.C. § 103(a) as obvious over, by Wu *et al.*, *Proc. Natl. Acad. Sci. USA* 86:9412-9416 (1989) (of record as Doc. No. 41 in Applicants' Information Disclosure Statement filed on September 17, 2001; hereinafter "Wu"). Applicants respectfully traverse these rejections.

In making these rejections, the Examiner essentially reiterates the contentions made above regarding Cheng stating that Wu discloses the recombinant production and sequencing of urate oxidase from baboon, mouse and pig, that "mammalian uricases are taught to tetramers" [sic] and that "the uricase can be recombinantly expressed and purified and the percent of non-tetrameric aggregates varied . . . ." Office Action at page 5, Section 9. Applicants respectfully disagree.

As the Examiner has noted, Wu mentions in passing that the uricase enzyme is localized predominately in liver and is associated with the peroxisome as a tetramer. *See* Wu at page 9412, col. 1. However, this passing statement in Wu is irrelevant since the present claims are drawn to an *isolated* uricase. As the present specification amply demonstrates, uricases form multimeric aggregates larger than tetramers upon isolation from their natural sources. *See, e.g.*, specification at page 16, and in Examples 1 and 2. These teachings of the present specification are supported by information that is readily available in the art. For

example, Alvares *et al.*, *Proc. Natl. Acad. Sci. USA* 89:4908-4912 (1992) (Doc. No. AR10 cited in Applicants' First Supplemental Information Disclosure Statement filed in the present matter on November 14, 2002) demonstrate that uricase *in vivo* is in an aggregated form that is so large as to be observable with an ordinary light microscope, in structures referred to by histologists as "crystalloid cores." *See* Alvares at p. 4908, in the Abstract and col. 2; and in Figures 4 and 5. Hence, the passing statement in Wu that uricases exist as tetramers in liver peroxisomes *in vivo* is not relevant to the patentability of the presently claimed *isolated* tetrameric uricases, particularly since the present specification and the art readily demonstrate that uricase *in vivo* is often present in aggregates that are much *larger* than the tetrameric form.

Moreover, Wu's analysis is strictly of the monomeric subunits of uricase, rather than the tetrameric form. Wu uses SDS/PAGE to analyze the uricases of pig, rat and mouse, reporting that the pig uricase is 32 kDa in size, compared to 33 kDa for rat and mouse uricases. The conditions of SDS/PAGE employed by Wu dissociate any uricase tetramers that might be present into the smaller 32-33 kDa monomeric subunits. As disclosed in the present specification at page 16, lines 5-7, tetrameric uricase is a 140 kDa protein. Hence, Wu clearly is identifying and comparing *monomeric* forms of uricase, rather than tetrameric forms, from pig, rat and mouse. Wu does not even mention purifying a tetrameric form of uricase, disclosing only the purification of uricase monomers. In addition, Wu only analyzes baboon uricase in a deduced amino acid sequence comparison of pig, mouse and baboon uricases and does not express the baboon protein. Wu's amino acid sequence comparison shows that the mouse urate oxidase open reading frame encodes a 303-amino acid polypeptide, while the pig

and baboon urate oxidase open reading frame encode a 304-amino acid polypeptide. As one of ordinary skill in the art would be readily aware, polypeptides having amino acid sequences of the length of those in Wu would be about 30-35 kDa in size. Hence, it is clear throughout this reference that Wu is analyzing uricase monomers and not uricase tetramers.

Furthermore, as discussed in detail above, simply because a uricase has been produced recombinantly and "purified" does not mean that that a given preparation of uricase contains tetrameric uricase to any particular level, let alone that it contains at least about 90% tetrameric uricase. Hence, without specifically purifying the uricase to enrich the preparation in the tetrameric form, the uricase preparations disclosed in Wu will contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. There is no express disclosure in Wu that the uricases disclosed therein were purified in such a way as to reduce the level of non-tetrameric uricase to no more than about 10%. In fact, the Examiner has pointed to no express disclosure in Wu that would support the statement in the present Office Action that the Wu uricases are "free of aggregates."

If instead the Examiner is basing this rejection upon the possible inherent disclosure of the claimed uricases in Wu, Applicants respectfully disagree with this approach. To rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). This burden has not been met in the present case, since the Examiner has pointed to no disclosure in Wu, nor any sound scientific reasoning, that uricases containing at least about 90% tetrameric uricase "necessarily flow"

from the disclosure in Wu. Indeed, as discussed in detail above, the present specification clearly shows that by preparing uricases according to the methods of Wu, but without undertaking the additional isolation procedures used to produce the presently claimed uricases, one of ordinary skill at best would succeed in preparing uricases that contain *less* than about 90% tetrameric uricase. Thus, any reliance upon inherent anticipation by Wu is factually and legally unfounded.

Accordingly, Wu does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b).

In addition, the Examiner's obviousness rejection over Wu essentially reiterates the contentions regarding Cheng in that "protein aggregation is an intrinsic property of the protein, and therefore obvious for one of ordinary skill in the art to vary the aggregation percent by varying the protein concentration . . . ." As discussed in detail above, it is thermodynamically unlikely that simply diluting the concentration of a uricase preparation will produce a preparation of uricase in which at least about 90% of the uricase is in the tetrameric form. In addition, one of ordinary skill would have to undertake undue experimentation, and would have had no reasonable expectation of success, to use a dilution approach to produce the claimed uricase preparations. Furthermore, as discussed fully above, the Examiner's contention that one of ordinary skill in the art would have been motivated to have combined Wu with what is well known in the art of protein chemistry to make the presently claimed isolated uricase tetramers is not based on any actual evidence or sound scientific reasoning available in the art. The Examiner has pointed to no express disclosure in Wu that would

support the Examiner's statement in the present Office Action that it would have been obvious to "vary the aggregation percent by varying the purified protein concentration." Therefore, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

In view of the foregoing remarks, Applicants respectfully assert that Wu does not anticipate, or in the alternative render obvious, claims 50-53 and 74-76 as currently presented. Reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102(b) or 103(a) over Wu therefore are respectfully requested.

***Conclusion***

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections, and allow all pending claims.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "Brian J. Del Buono", with a long horizontal flourish extending to the right.

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